IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Applicant	:	Liang C. Dong	
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Art Unit	:	1615	
Examiner	:	Young, Micah Paul	
Docket No.	:	ARC3244R1	
Customer No.	:	30766	
Title	:	Formulation and Dosage Form Providing Increased Bioavailability of Hydrophobic Drugs	

Mail Stop Amendment
Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT

Sir:

In response to the Office Action dated January 12, 2007, kindly amend the application identified above as follows:

AMENDMENTS TO THE CLAIMS are reflected in the listing of claims which begins on page 2 of this paper.

REMARKS/ARGUMENTS begin on page 9 of this paper.

AMENDMENTS TO THE CLAIMS:

This listing of claims will replace all prior versions, and listings, of claims in the application:

LISTING OF CLAIMS

1. (original) A drug formulation comprising:

a hydrophobic drug in nanoparticulate form;

an oil phase comprising a saturated fatty acid; and

a surfactant, wherein the surfactant and saturated fatty acid are selected and combined such that the drug formulation automatically forms a stable emulsion upon introduction to an aqueous media.

2. (original) The drug formulation of claim 1, wherein the hydrophobic drug comprises a drug classified as a Class II drug under the Biopharmaceutics Classification System.

3. (original) The drug formulation of claim 1, wherein the hydrophobic drug exhibits a dose/solubility volume of more than 250 ml.

4. (original) The drug formulation of claim 1, wherein the hydrophobic drug comprises particles of hydrophobic drug that are smaller than about 1 μm in all dimensions.

5. (original) The drug formulation of claim 1, wherein the hydrophobic drug comprises particles of hydrophobic drug that are smaller than about 0.5 μm in all dimensions.

6. (original) The drug formulation of claim 1, wherein the hydrophobic drug comprises particles of hydrophobic drug that are smaller than about 0.2 μm in all dimensions.

7. (original) The drug formulation of claim 1, wherein the hydrophobic drug comprises a drug selected from the group consisting of antibacterial agents, antiviral agents, anti-fungal agents, antacids, anti-inflammatory substances, coronary vasodilators, cerebral vasodilators, psychotropics, antineoplastics, stimulants, antihistamines, laxatives, decongestants, vitamins,

anti-diarrheal preparations, anti-anginal agents, vasodilators, anti-arrythmics, anti-hypertensives, vasoconstrictors, anti-migraine drugs, antineoplastic drugs, anticoagulants, anti-thrombotic drugs, analgesics, anti-pyretics, neuromuscular agents, agents acting on the central nervous system, hyperglycemic agents, hypoglycemic agents, thyroid and anti- thyroid preparations, diuretics, anti-spasmodics, uterine relaxants, mineral and nutritional additives, anti- obesity agents, anabolic agents, ani-asthmatics, expectorants, cough suppressants, mucolytics, and anti-uricemic drugs

8. (original) The drug formulation of claim 1, wherein the hydrophobic drug comprises a drug selected from the group consisting of poorly soluble proteins, polypeptides, peptides, proteomimetic and peptidomimetic materials.

9. (original) The drug formulation of claim 1, wherein the fatty acid comprises a saturated C8 through a C12 fatty acid.

10. (original) The drug formulation of claim 1, wherein the fatty acid comprises a saturated C10 fatty acid.

11. (original) The drug formulation of claim 1, wherein the fatty acid comprises capric acid.

12. (original) The drug formulation of claim 1, wherein the fatty acid comprises a blend of fatty acids selected from saturated C8 through C12 fatty acids.

13. (original) The drug formulation of claim 1, wherein the fatty acid comprises 10 wt% to 80 wt% of the drug formulation.

14. (original) The drug formulation of claim 1, wherein the fatty acid comprises 35 wt% to 45 wt% of the drug formulation.

15. (currently amended) The drug formulation of claim 1, wherein the hydrophobic drug

comprises a drug that exhibits a solubility in the oil phase that is at least 10 times greater than the solubility of the drug in water.

16. (currently amended) The drug formulation of claim 1, wherein the hydrophobic drug comprises a drug that exhibits a solubility in the oil phase that is at least 100 times greater than the solubility of the drug in water.

17. (currently amended) The drug formulation of claim 1, wherein the hydrophobic drug comprises a drug that exhibits a solubility in the oil phase that is at least 500 times greater than the solubility of the drug in water.

18. (original) The drug formulation of claim 1, wherein the hydrophobic drug comprises from 2 wt% to 50 wt% of the drug formulation.

19. (original) The drug formulation of claim 1, wherein the drug formulation comprises a first amount of hydrophobic drug dissolved within the oil phase and a second amount of hydrophobic drug suspended as a nanoparticulate material, with the first amount of hydrophobic drug and the second amount of hydrophobic drug accounting for 2 wt% to 50 wt% of the drug formulation.

20. (original) The drug formulation of claim 1, wherein the hydrophobic drug comprises from 10 wt% to about 30 wt% of the drug formulation.

21. (original) The drug formulation of claim 1, wherein the drug formulation comprises a first amount of hydrophobic drug dissolved within the oil phase and a second amount of hydrophobic drug suspended as a nanoparticulate material, with the first amount of hydrophobic drug and the second amount of hydrophobic drug accounting for 10 wt% to 30 wt% of the drug formulation.

22. (original) The drug formulation of claim 1, wherein the surfactant comprises a non-ionic surfactant.

23. (original) The drug formulation of claim 1, wherein the surfactant comprises a non-ionic surfactant and accounts for 5 wt% to 90 wt% of the drug formulation.

24. (original) The drug formulation of claim 1, wherein the surfactant comprises a non-ionic surfactant and accounts for 25 wt% to 45 wt% of the drug formulation.

25. (original) The drug formulation of claim 1, wherein the surfactant is selected from the group consisting of polyoxyethylene products of hydrogenated vegetable oils, polyethoxylated castor oils, polyethoxylated hydrogenated castor oils, polyoxyehtylene sorbitan-fatty acid esters, polyoxyethylene castor oil derivatives, and pluronic surfactants.

26. (currently amended) The drug formulation of claim 1, wherein the ~~surfacant~~ surfactant is selected from the group consisting of polyoxyethylenated castor oil comprising 9 moles of ethylene oxide, polyoxyethylenated castor oil comprising 15 moles of ethylene oxide, polyoxyethylenated castor oil comprising 25 moles of ethylene oxide, polyoxyethylenated castor oil comprising 35 moles of ethylene oxide, polyoxyethylene castor oil comprising 40 moles of ethylene oxide, polyoxylenated castor oil comprising 52 moles of ethylene oxide, polyoxyethylenated sorbitan monopalmitate comprising 20 moles of ethylene oxide, polyoxyethylenated sorbitan monostearate comprising 20 moles of ethylene oxide, polyoxyethylenated sorbitan monostearate comprising 4 moles of ethylene oxide, polyoxyethylenated sorbitan tristearate comprising 20 moles of ethylene oxide, polyoxyethylenated sorbitan monostearate comprising 20 moles of ethylene oxide, polyoxyethylenated sorbitan trioleate comprising 20 moles of ethylene oxide, polyoxyethylenated stearic acid comprising 8 moles of ethylene oxide, polyoxyethylene lauryl ether, polyoxyethylenated stearic acid comprising 40 moles of ethylene oxide, polyoxyethylenated stearic acid comprising 50 moles of ethylene oxide, polyoxyethylenated stearyl alcohol comprising 2 moles of ethylene oxide, and polyoxyethylenated oleyl alcohol comprising 2 moles of ethylene oxide.

27. (currently amended) The drug formulation of claim 1, wherein the surfactant is selected

from the group consisting of NIKKOL HCO-50® (PEG-60 Hydrogenated Castor Oil), NIKKOL HCO-35® NIKKOL HCO-40® (PEG-40 Hydrogenated Castor Oil), NIKKOL HCO-60® (PEG-60 Hydrogenated Castor Oil), CREMAPHORE® (PEG Hydrogenated Castor Oil), CREMAPHORE RH40® (PEG-40 Hydrogenated Castor Oil), CREMAPHORE RH60® (PEG-60 Hydrogenated Castor Oil), CREMAPHORE RH410® (PEG-40 Hydrogenated Castor Oil), CREMAPHORE RH455® (PEG-40 Hydrogenated Castor Oil with Propylene Glycol), and CREMAPHORE EL® (PEG-35 Castor Oil), TWEEN 20® (Polysorbate 20), TWEEN 21® (Polysorbate 21), TWEEN 40® (Polysorbate 40), TWEEN 60® (Polysorbate 60), TWEEN 80® (Polysorbate 80), TWEEN 81® (Polysorbate 81), Pluronic F68, Pluronic F108, and Pluronic F127.

28. (original) The drug formulation of claim 1, wherein the surfactant is included in the drug formulation in an amount sufficient to cause the drug formulation to automatically form a stable microemulsion upon introduction to an aqueous media.

29. (original) A drug formulation formed of a nanosuspension of a hydrophobic drug, the drug formulation comprising:

a hydrophobic drug material in nanoparticulate form;

an oil phase comprising a saturated C8 through a C12 fatty acid, wherein the hydrophobic drug material exhibits a solubility in the oil phase that is at least 10 times greater than the solubility of the hydrophobic drug material in water; and

a non-ionic surfactant, wherein the non-ionic surfactant and oil phase are selected and combined such that the drug formulation automatically forms a stable emulsion upon introduction to an aqueous media.

30. (original) The drug formulation of claim 29, wherein hydrophobic drug comprises a drug classified as a Class II drug under the Biopharmaceutics Classification System, the drug 20 exhibiting a dose/solubility volume of more than 250 ml.

31. (original) The drug formulation of claim 30, wherein the hydrophobic drug is selected from the group consisting of hydrophobic drug materials exhibiting an average particle size that

is smaller than about 1 μm in all dimensions, hydrophobic drug materials exhibiting an average particle size that is smaller than about 0.5 sum in all dimensions, and hydrophobic drug materials exhibiting an average particle size that is smaller than about 0.2 μm in all dimensions.

32. (currently amended) The drug formulation of claim [[1]] 29, wherein the fatty acid comprises 35 wt% to 45 wt% of the drug formulation, and the non-ionic surfactant comprises 25 wt% to 45 wt% of the drug formulation.

33. (currently amended) The drug formulation of claim 32, ~~wherein the~~ wherein the drug formulation comprises a first amount of hydrophobic drug dissolved within the oil phase and a second amount of hydrophobic drug suspended as a nanoparticulate material, with the first amount of hydrophobic drug and the second amount of hydrophobic drug accounting for 10 wt% to 40 wt% of the drug formulation.

34. (original) The drug formulation of claim 29, wherein the surfactant is included in the drug formulation in an amount sufficient to cause the drug formulation to automatically form a stable microemulsion upon introduction to an aqueous media.

35. (original) A drug formulation formed of a nanosuspension of a hydrophobic drug, the drug formulation comprising:

a hydrophobic drug material in nanoparticulate form, wherein the hydrophobic drug material comprises a drug exhibiting a dose/solubility volume of more than 250 ml and is selected from the group consisting of hydrophobic drug materials exhibiting an average particle size that is smaller than about 1 μm in all dimensions, hydrophobic drug materials exhibiting an average particle size that is smaller than about 0.5 μm in all dimensions, and hydrophobic drug materials exhibiting an average particle size that is smaller than about 0.2 μm in all dimensions;

an oil phase comprising a saturated C8 through a C12 fatty acid, wherein the hydrophobic drug material exhibits a solubility in the oil phase that is at least 100 times greater than the solubility of the hydrophobic drug material in water; and

a non-ionic surfactant, wherein the non-ionic surfactant and oil phase are selected and combined such that the drug formulation automatically forms a stable microemulsion upon introduction to an aqueous media.

36. (original) The drug formulation of claim 35, wherein the fatty acid comprises 35 wt% to 45 wt% of the drug formulation, and the non-ionic surfactant comprises 25 wt% to 45 wt% of the drug formulation.

37. (original) The drug formulation of claim 36, wherein the drug formulation comprises a first amount of hydrophobic drug dissolved within the oil phase and a second amount of hydrophobic drug suspended as a nanoparticulate material, with the first amount of hydrophobic drug and the second amount of hydrophobic drug accounting for 10 wt% to 40 wt% of the drug formulation.

38. (original) The drug formulation of claim 1, wherein the hydrophobic drug, the oil phase, and the surfactant are selected and combined such that the drug formulation provides at least a four-fold increase in the bioavailability of the hydrophobic drug when delivered from a controlled release dosage form relative to a tableted, immediate release formulation of the drug.

39. (original) The drug formulation of claim 29, wherein the hydrophobic drug, the oil phase, and the surfactant are selected and combined such that the drug formulation provides at least a four-fold increase in the bioavailability of the hydrophobic drug when delivered from a controlled release dosage form relative to a tableted, immediate release formulation of the drug.

40. (original) The drug formulation of claim 35, wherein the hydrophobic drug, the oil phase, and the surfactant are selected and combined such that the drug formulation provides at least a four-fold increase in the bioavailability of the hydrophobic drug when delivered from a controlled release dosage form relative to a tableted, immediate release formulation of the drug.

REMARKS/ARGUMENTS

Favorable reconsideration of this application is requested in view of the amendments above and the remarks which follow.

DISPOSITION OF CLAIMS

Claims 1-40 are pending in this application. The claims have been amended as set forth above to correct informalities.

REJECTIONS UNDER 35 U.S.C. §112

Claims 19, 21, 27, 32, and 37 were rejected under 35 USC 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Withdrawal of this rejection is respectfully requested in view the following remarks.

Claim 19 has been amended to include chemical names of the surfactants previously identified solely by their trademarks/trade names.

Claim 32 has been amended to depend from claim 29, which provides antecedent basis for the term "non-ionic surfactant."

With respect to claims 19, 21, 33, and 37, the Examiner asks how a drug can be partially dissolved in the same medium without a solvent present in the emulsion. It is important to note that claims 19, 21, 33, and 37 are directed to a self-emulsifying formulation, not an emulsion. The self-emulsifying formulation does not become an emulsion until it is introduced into an aqueous media. The hydrophobic drug is soluble in the oil phase of the self-emulsifying formulation. Since the oil phase dissolves the hydrophobic drug, the oil phase functions as a solubilizer/solvent for the hydrophobic drug. It is possible to have both solubilized and solid nanoparticles of the hydrophobic drug in the self-emulsifying formulation during and/or after preparation if the drug loading exceeds the drug solubility in the self-emulsifying formulation. In this example, the solubilized drug would provide high solubility after emulsification in an aqueous medium, while the nanoparticles would impart rapid dissolution.

REJECTIONS UNDER 35 U.S.C. §102

I. Claims 1, 2, 4-7, 9-14, 18, 22, 23, 25-28, 38, and 39 stand rejected under 35 U.S.C. 102(b) as being anticipated by Aviv et al. (U.S. Patent No. 5,496,811). This rejection is respectfully traversed.

Aviv et al disclose an oil-in-water emulsion comprising a hydrophobic drug, an oily phase, a surfactant/emulsifier, and an aqueous component, where the mean droplet size of the oil phase is in a range from 0.05 to 0.5 microns. The submicron droplets are formed only after incorporating the drug and surfactant/emulsifier in an oil phase and dispersing the oil phase in an aqueous component. The examples describe subjecting the oil-in-water emulsion to additional processes to form the submicron droplets. Aviv et al neither disclose nor teach that the hydrophobic drug is in nanoparticulate form prior to forming the oil-in-water emulsion. It should be noted that the formulation recited in the claims has not been introduced into an aqueous media, is not an oil-in-water emulsion, and does not form an oil-in-water emulsion until introduced into an aqueous media. Stable nanosuspension in self-emulsifying formulation gives rise to high drug loading and rapid dissolution.

From the foregoing, Aviv et al do not anticipate the invention as recited in claims 1, 2, 4-7, 9-14, 18, 22, 23, 25-28, 38, and 39. Withdrawal of the rejection of claims 1, 2, 4-7, 9-14, 18, 22, 23, 25-28, 38, and 39 in view of Aviv et al. is respectfully requested.

II. Claims 1, 2, 4-14, 18, 22, 23, 25-28, 38, and 39 were rejected under 35 USC 102(b) as being anticipated by Friedman et al (U.S. Patent No. 6,113,921). This rejection is respectfully traversed.

Friedman et al. teach a pharmaceutical composition comprising submicron droplets of a water-insoluble drug. Each droplet includes an oily liquid comprising the drug, an emulsifier, and a surfactant. The submicron droplets are formed only after incorporating the drug and surfactant/emulsifier in an oil phase and dispersing the oil phase in an aqueous phase. The examples describe subjecting the oil-in-water emulsion to additional processes to form the submicron droplets. Friedman et al neither disclose nor teach that the water-insoluble drug is in nanoparticulate form prior to forming the oil-in-water emulsion. It should be noted that the formulation recited in the claims has not been introduced into an aqueous media, is not an oil-in-water emulsion, and does not form an oil-in-water emulsion until introduced into an aqueous

media. Stable nanosuspension in self-emulsifying formulation gives rise to high drug loading and rapid dissolution.

From the foregoing, Friedman et al do not anticipate the invention as recited in claims 1, 2, 4-14, 18, 22, 23, 25-28, 38, and 39. Withdrawal of the rejection of claims 1, 2, 4-14, 18, 22, 23, 25-28, 38, and 39 in view of Friedman et al is respectfully requested.

III. Claims 1-6, 9-31, 34-36, and 38-40 were rejected under 35 U.S.C. 102(b) as being anticipated by Yiv et al (U.S. Patent No. 6,245,349). This rejection is respectfully traversed.

Yiv et al disclose a drug formulation including a drug, a phospholipid component, a polypropylene glycol, a high HLB surfactant, and optionally water and/or oil. In concentrate form, the drug formulation does not include water. In diluted form, the drug formulation includes water. The diluted drug formulations are referred to as oil-in-water emulsions. Yiv et al disclose that the diluted drug formulation is such that it is filter sterilizable. Filter sterilization includes passing the composition through a 0.22 micron filter. Submicron average particle sizes are reported for the diluted drug formulation but not for the concentrated drug formulation. Yiv et al neither disclose nor teach that the drug is in nanoparticulate form in the concentrated drug formulation. It should be noted that the formulation recited in the claims has not been introduced into an aqueous media, is not an oil-in-water emulsion, and does not form an oil-in-water emulsion until introduced into an aqueous media. Stable nanosuspension in self-emulsifying formulation gives rise to high drug loading and rapid dissolution.

From the foregoing, Yiv et al do not anticipate the invention as recited in claims 1-6, 9-31, 34-36, and 38-40. Withdrawal of the rejection of claims 1-6, 9-31, 34-36, and 38-40 in view of Yiv et al is respectfully requested.

CONCLUSION

Applicant believes that this paper is fully responsive to the Office Action dated January 12, 2007, and respectfully requests that a timely Notice of Allowance be issued in this case.

Please apply any charges not covered or credits in connection with this filing to Deposit Account No. 50-3202 (ref. ARC3244R1).

Respectfully submitted,

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